RESEARCH ARTICLE

Genetic Variants at 6p21.1 and 7p15.3 Identified by GWASs of Multiple Cancers and Ovarian Cancer Risk: a Case-control Study in Han Chinese Women

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Abstract

A recent study summarized several published genome-wide association studies (GWASs) of cancer and reported two pleiotropic loci at 6p21.1 and 7p15.3 contributing to multiple cancers including lung cancer, noncardia gastric cancer (NCGC), and esophageal squamous-cell carcinoma (ESCC) in Han Chinese. However, it is not known whether such genetic variants have similar effects on the risk of gynecologic cancers, such as ovarian cancer. Hence, we explored associations between genetic variants in 6p21.1 and 7p15.3 and ovarian cancer risk in Han Chinese women. We performed an independent case-control study by genotyping the two loci (rs2494938 A > G at 6p21.1 and rs2285947 A > G at 7p15.3) in a total of 377 ovarian cancer cases and 1,034 cancer-free controls using TaqMan allelic discrimination assay. We found that rs2285947 at 7p15.3 was significantly associated with risk of ovarian cancer with per allele odds ratio (OR) of 1.33 [95% confidence interval (CI): 1.08-1.64, *P*=0.008]. However, no significant association was observed between rs2494938 and ovarian cancer risk. Our results showed that rs2285947 at 7p15.3 may also contribute to the development of ovarian cancer in Han Chinese women, further suggesting pleiotropy of 7p15.3 in multiple cancers.

Keywords: Ovarian cancer - Chinese women - GWASs - single nucleotide polymorphism - 7p15.3

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Introduction

Ovarian cancer is the leading cause of death from gynecologic cancer in women worldwide (Kumar et al., 2011), with an estimation of 225,500 women diagnosed with ovarian cancer and 140,200 deaths in 2008 (Lowe et al., 2013). Several risk factors of ovarian cancer have already been identified, such as parity (Pasalich et al., 2013), never breastfeeding (Luan et al., 2013), endometriosis (Vargas-Hernandez 2013), tubal ligation (Cramer 2012), body mass index and height (BMI) (Olsen et al., 2013) and family history (Moorman et al., 2013). Furthermore, there is growing evidence suggesting that genetic variants may contribute to the susceptibility to ovarian cancer (Mohamed et al., 2013; Shen et al., 2013). Over the last several years, as a powerful method to investigate the genetic determinants of complex diseases, genome-wide association studies (GWASs) have successfully identified many genetic markers for susceptibility to cancers (Yang et al., 2013). Meanwhile, pleiotropy has been observed for several loci, such as the regions of 8q24 (Pomerantz et al., 2009; Tuupanen et al., 2009), 5p15.33 (TERT-CLPTM1L) (Rafnar et al., 2009) and 9p21.3 (ANRIL) (Bishop et al., 2009; Stacey et al., 2009; Turnbull et al., 2010).

Recently, Jin et al. (2012) synthesized the data from several published GWASs of multiple cancers in Han Chinese, including lung cancer, non-cardia gastric cancer (NCGC), and esophageal squamous-cell carcinoma (ESCC), and identified two new susceptible loci (rs2494938 at 6p21.1 and rs2285947 at 7p15.3) associated with risks of multiple cancers (Jin et al., 2012), implying the pleiotropy of genetic variants in these two regions. However, the role of genetic variants at 6p21.1 and 7p15.3 is unknown in the development of female-specific cancers, such as ovarian cancer. In this study, we conducted a case-control study with 377 cases and 1034 controls to explore the relationship of two loci (rs2494938 A > G at 6p21.1 and rs2285947 A > G at 7p15.3) with ovarian cancer risk in Han Chinese woman.

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Table 1. Information of Primers and Probes for TaqMan Allelic Discrimination

Polymorphisms	Sequence(5'-3')
rs2494938	
Primer	F:GGCCTGGGATCTATGTGTCTAAGA
	R:AGAACCGTCTAAGAGTCTCCTTGAT
Probe	A: AGACAGCAACTTCTC
	G: ACAGCAGCTTCTC
rs2285947	
Primer	F: TCTTTTGTTTTAGGACTCTCCTAAT TGTAACTTTAA
	R:AGTCATTCCATTGAACATTATAATAA CTATTTAACTTAGGT
Probe	A: TAGACAAGGCAATAGAAC
	G: ACAAGGCGATAGAAC

Materials and Methods

Study population

This case-control study was approved by the institutional review board of Nanjing Medical University. Ovarian cancer cases were recruited in the areas with relatively high incidence, including cities of Nantong, Wuxi and Nanjing from Jiangsu province, eastern China. All the 377 ovarian cancer cases had definite pathological diagnosis. The criteria for the recruitment of ovarian cancer cases included: (1) Han Chinese; (2) local residences (at least 5 years); (3) without previous malignant tumor in any other organs; (4) histopathologically confirmed diagnosis.

During the same period as the cases were recruited, cancer-free women in the control group were randomly selected from a cohort of more than 30, 000 participants in a community-based screening program for non-infectious diseases conducted in Jiangsu Province (Jiang et al., 2011). All subjects were genetically unrelated, ethnic Han Chinese women. Each individual was interviewed face-to-face by trained interviewers to get demographic information, age at menarche, menstrual and reproduction history and environmental exposure history. Approximately 5ml venous blood sample was obtained from each subject. Eventually, 377 ovarian cancer cases and 1034 cancer-free controls frequency matched by age (5 years age categories) were included in this study.

Genotyping

Genotyping was conducted by using the TaqMan allelic discrimination assay on ABI PRISM 7900 HT platform (Life Technologies. CarIsbad USA). Information of the primers and probes were shown in Table 1. Experimental conductor was not informed the subjects' case or control status. In each 384-well reaction plate, two negative controls were added for quality control. The genotype data were analyzed by using SDS 2.3 Allelic Discrimination Software (Applied Biosystems). To make sure the genotyping results, 50 cases and 50 controls were randomly selected to repeat, yielding a 100% concordant.

Table 2. Demographic and Selected Variables for Ovarian Cancer Cases and Controls

Variables	Case (N =377)	Control (N=1034)	P^a
Age, year (mean ± SD[e])	52.42±12.20	52.75±11.91	0.813
Age at menarche, year (mean ± SD)	14.69±1.50	16.13±1.20	<0.001
Abortion[b]			<0.001
Yes	204	686	
No	153	257	
Menopausal status[c]			<0.001
Premenopausal	126	465	
Natural menopause	224	546	
Histological type			
Epithelial	327		
Other types[d]	50		
Stage			
I or II	103		
III or IV	274		

[a]T-tests and χ^2 tests were used for continuous or categorical variables, respectively; [b]20 cases and 91 controls were without information; [c]27 cases and 23 controls were without information; [d]Other types included germ cell type and sex cord stromal type; [e]Standard Deviation

Statistical analyses

χ^2 test (for categorical variables) and student t test (for continuous variables) were used for evaluating the differences in the distributions of demographic characteristics, selected variables, and frequencies of genotypes between the cases and controls. Logistic regression analysis was applied for estimating the association between genotypes and ovarian cancer risk with adjustment for age, age at menarche, menopausal status, and abortion information. Hardy-Weinberg equilibrium was tested using goodness-of-fit χ^2 test. All of the statistical analyses were performed with Statistical Analysis System software (9.1.3; SAS Institute, Cary, NC).

Results

Characteristics of ovarian cancer cases and cancer-free controls are shown in Table 2. In 377 ovarian cancer patients, 327 were diagnosed as epithelial ovarian cancers, and 55 were reported as other pathological types. Nearly 72.7% (274) patients were diagnosed at stage III or IV and 27.3% (103) were at stage I or II. The age was comparable between cases and controls (P>0.05). However, ovarian cancer cases had earlier menarche age, more abortion history and more premenopausal status compared with cancer-free controls (all P<0.05).

Table 3. The Locus and Genotyping Information for Selected Snps at 6P21.1 and 7P15.3

SNP	Chromosome	Position	Location	Major/Minor allele	Call rate	HWE[a]	MAF[b]
rs2494938	6p21.1	40,536,128	Intron of LRFN2	G>A	99.30%	0.48	0.24/0.26
rs2285947	7p15.3	21,584,088	Intron of DNAH11	G>A	99.40%	0.67	0.29/0.23

[a]P values for Hardy-Weinberg equilibrium(HWE) tests; [b]Minor allele frequency(MAF) in cases/controls; [c]Adjusted by age , age at menarche, menopause status and abortion information

Table 4. Main Effects of Rs2494938 at 6P21.1 and Rs2285947 at 7P15.3 on Ovarian Cancer Risk

Genotypes	Cases (%)	Controls (%)	Crude OR (95%CI)	Crude P	Adjusted OR (95%CI)[a]	Adjusted P^a
rs2285947						
GG	186 (50.13)	607 (58.87)	1		1	
AG	155 (41.78)	365 (35.40)	1.39 (1.08-1.78)	1.00×10^{-2}	1.44 (1.09-1.87)	9.90×10^{-3}
AA	30 (8.09)	59 (5.72)	1.66 (1.04-2.66)	3.38×10^{-2}	1.55 (0.91-2.63)	1.07×10^{-1}
Dominant model			1.43 (1.12-1.81)	3.50×10^{-3}	1.45 (1.11-1.89)	5.70×10^{-3}
Additive model			1.33 (1.10-1.61)	2.80×10^{-3}	1.33 (1.08-1.64)	7.70×10^{-3}
rs2494938						
GG	209 (56.64)	556 (53.88)	1		1	
AG	140 (37.94)	409 (39.63)	0.91 (0.71-1.17)	4.62×10^{-1}	0.89 (0.68-1.17)	4.01×10^{-1}
AA	20 (5.42)	67 (6.49)	0.79 (0.47-1.34)	3.89×10^{-1}	0.69 (0.38-1.27)	2.34×10^{-1}
Dominant model			0.89 (0.70-1.14)	3.60×10^{-1}	0.86 (0.66-1.12)	2.70×10^{-1}
Additive model			0.90 (0.74-1.10)	3.01×10^{-1}	0.86 (0.69-1.08)	1.89×10^{-1}

[a]Adjusted by age , age at menarche, menopause status and abortion information

Table 5. Stratified Analysis on the Associations Between Rs2494938/Rs2285947 and Risk of Ovarian Cancer

SNPs	Cases						Controls						OR(95%CI)[a]	P^a	P^b
Variables	AA	(%)	AG	(%)	GG	(%)	AA	(%)	AG	(%)	GG	(%)			
Rs2494938															
Age															
<52	8	4.71%	70	41.18%	92	54.12%	31	6.11%	201	39.64%	275	54.24%	0.97(0.66-1.42)	0.132	0.412
≥52	12	6.03%	70	35.18%	117	58.79%	36	6.86%	208	39.62%	281	53.52%	0.77(0.53-1.11)	0.159	
Age at menarche															
<15	7	4.19%	62	37.13%	98	58.68%	13	5.80%	95	42.41%	116	51.79%	0.72(0.46-1.12)	0.142	0.348
≥15	11	5.98%	72	39.13%	101	54.89%	54	6.71%	313	38.88%	438	54.41%	0.94(0.67-1.31)	0.696	
Abortion															
Yes	9	5.96%	49	32.45%	93	61.59%	14	5.47%	107	41.80%	135	52.73%	0.66(0.43-1.03)	0.069	0.142
No	8	4.04%	84	42.42%	106	53.54%	49	7.15%	265	38.69%	371	54.16%	1.00(0.72-1.40)	0.983	
Menopausal status															
Premenopausal	7	5.74%	41	33.61%	74	60.66%	32	6.88%	191	41.08%	242	52.04%	0.73(0.47-1.11)	0.143	0.39
Postmenopausal	12	5.38%	88	39.46%	123	55.16%	35	6.42%	209	38.35%	301	55.23%	0.93(0.66-1.31)	0.687	
Rs2285947															
Age															
<52	11	6.43%	75	43.86%	85	49.71%	30	5.93%	171	33.79%	305	60.28%	1.28(0.94-1.75)	0.114	0.754
≥52	19	9.50%	80	40.00%	101	50.50%	29	5.52%	194	36.95%	302	57.52%	1.37(1.03-1.84)	0.032	
Age at menarche															
<15	14	8.33%	72	42.86%	82	48.81%	14	6.25%	86	38.39%	124	55.36%	1.21(0.86-1.70)	0.284	0.45
≥15	15	8.11%	78	42.16%	92	49.73%	45	5.59%	277	34.41%	483	60.00%	1.43(1.09-1.86)	0.009	
Abortion															
Yes	19	9.41%	84	41.58%	99	49.01%	40	5.85%	250	36.55%	394	57.60%	1.28(0.98-1.67)	0.066	0.646
No	8	5.37%	68	45.64%	73	48.99%	14	5.47%	87	33.98%	155	60.55%	1.42(1.00-2.03)	0.051	
Menopausal status															
Premenopausal	9	7.32%	55	44.72%	59	47.97%	21	4.53%	155	33.41%	288	62.07%	1.57(1.12-2.21)	0.009	0.21
Postmenopausal	19	8.48%	94	41.96%	111	49.55%	35	6.41%	200	36.63%	311	56.96%	1.19(0.91-1.56)	0.205	

[a]Per allele Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, age at menarche, abortion and menopausal status where appropriate; [b]*P* for heterogeneity test

Loci and genotyping information of the two loci (rs2494938 and rs2285947) are presented in Table 3. Call rates of the two loci were above 99% and the genotype frequencies of the two loci in the control subjects were consistent with Hardy–Weinberg equilibrium ($P>0.05$). As shown in Table 4, a significant association was observed between rs2285947 and ovarian cancer risk (dominant model: adjusted OR=1.45, 95%CI 1.11-1.89, $P=0.006$; additive model: adjusted OR=1.33, 95%CI 1.08-1.64, $P=0.008$,). However, no significant association was found between rs2494938 and ovarian cancer risk (dominant model: adjusted OR=0.86, 95%CI 0.66-1.12, $P=0.270$; additive model: adjusted OR=0.86, 95%CI 0.69-1.08, $P=0.190$) (Table 4).

Additionally, we conducted stratification analyses to evaluate the potential association between the two SNPs (rs2494938/rs2285947) and ovarian cancer risks stratified by age, age at menarche, abortion history, and menopausal status (Table 5). The results showed that associations between rs2285947 and ovarian cancer risk were significant in the subgroups with age above 52 years old (additive model: OR=1.37, 95%CI 1.03-1.84-1.75, $P=0.032$), with age at menarche over 15 years old (additive model: OR= 1.43, 95%CI 1.09-1.86, $P=0.009$) and premenopausal women (additive model: OR=1.57, 95%CI 1.12-2.21, $P = 0.009$). However, no significant heterogeneity was detected between the stratified subgroups. Furthermore, no significant result was found for the association between rs2494938 and ovarian cancer risk in every stratum (Table 5).

Discussion

In the present case-control study, we investigated the relationship between two loci at 6p21.1 and 7p15.3 identified by the GWAS of multiple cancers and ovarian

cancer risk and found that rs2285947 at 7p15.3 was significantly associated with ovarian cancer risk in Han Chinese women.

Rs2285947 is located at 7p15.3 in the intron of DNAH11 gene (Dynein, axonemal, heavy chain)[MIM603339] and SNPs (Single Nucleotide Polymorphisms) in strong linkage disequilibriumLD with rs2285947 are located in the initial parts of both SP4 (Specificity Protein 4[MIM 600540]) and DNAH11. By using publicly available data of cis-expression quantitative trait loci (eQTLs), we found that a SNP rs7788515 in strong LD with rs2285947 (r^2=0.92) plays a role in the expression of DNAH11 (P=5.40×10^{-7}) (Ge et al., 2009). Dyneins are microtubule-associated motor protein complexes and has been reported that in vivo it is necessary for the activation of MAPK (mitogen-activated protein kinase) kinase3/6 and p38 (Cheung et al., 2004). The p38-MAPK pathway plays important roles in the regulation of several biological progresses including cell survival, differentiation, migration (Cuenda et al., 2007; Cuadrado et al., 2010), immune and inflammatory responses (Han et al., 1994; Lee et al., 1994). Our study showed that rs2285947 A allele was associated with an increased risk of ovarian cancer risk in Han Chinese women, consistent with the findings in lung cancer, non-cardia gastric cancer, and esophageal squamous-cell carcinoma by Jin et al. (2012). Furthermore, it has been reported that several other loci at 7p15.3 were associated with many kinds of cancers, such as multiple myeloma (rs4487645) (Broderick et al., 2012; Martino et al., 2012) and lung cancer (rs2710994) (Xun et al., 2011), and DNA copy number aberrations (DCNAs) at 7p15.3 increased the risk of invasive cervical carcinoma (Oh et al., 2012). All these findings provided evidence that genetic variants at 7p15.3 are potentially important susceptibility loci associated with the development of multiple cancers. Further investigations are necessary to identify the specific mechanism of such loci/gene in the development of human cancer.

Rs2494938 is located at 6p21.1 in the intron one of LRFN2 [MM612808] (encoding leucine-rich repeat and fibronectin type III domain-containing protein 2). It has been reported that the LRFN2 in cooperation with MYC lead to erythroblastosis (Castellanos et al., 2007). LRFN2 is a member of synaptic adhesion-like molecule (SALMs) and the family is associated with the N-methyl D-aspartate (NMDA) receptors (Wang et al., 2006). Some evidences had shown that the NMDA receptor 2B is methylated in ESCC and non-small cell lung cancer, exhibiting a tumor-suppressive activity (Kim et al., 2006; Tamura et al., 2011). Jin et al. (2012) reported that A allele significantly increased the risk of multiple cancers including lung cancer, non-cardia gastric cancer, and esophageal squamous-cell carcinoma. However, in the current study, we could not validate the association between rs2494938 at 6p21.1 and ovarian cancer risk, indicating that these loci may have no effect on the development of ovarian cancer.

In this study, several limitations need to be addressed. First, the statistical power was relatively low due to the small sample size, which may miss the real association between loci at 6p21.1 and ovarian cancer risk. Second, the biological mechanism of genetic variants at 7p15.3 was not further investigated in this study. In general, our results indicated that the positive associations between genetic variants at 7p15.3 and multiple types of cancer are also reduplicative in ovarian cancer in Chinese women. The functional relevance of genetic variants in 7p15.3 and the role in susceptibility to ovarian cancer remain to be confirmed in larger epidemiological studies and in-depth mechanistic studies.

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